NTP
National Toxicology Program

Draft NTP Technical Report TR 572 on
Methyl *trans*-Styryl Ketone

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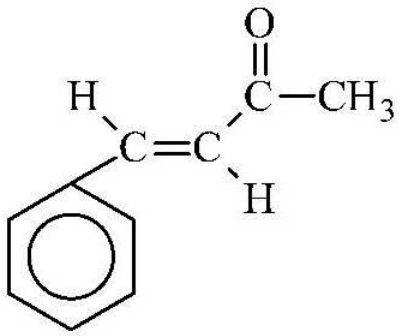
Methyl *trans*-styryl ketone (MSK)

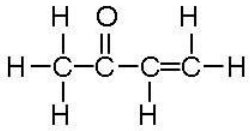


Rationale for testing

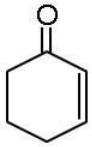
- Nominated by NCI as a member of the structural class of α,β-unsaturated ketones
- Human exposure as a synthetic flavoring agent (0.02-5.2 ppm)
- Human exposure as a synthetic fragrance agent (50-500 ppm)
- Positive mutagenicity data in Ames/*Salmonella* and mouse lymphoma assays
- NB: The CAS # 122-57-6 is for mixed isomers of methyl styryl ketone and is not used in this study; the CAS # 1896-62-4 specifies the *trans* isomer used in this study

Compounds studied under the α, β-unsaturated ketone initiative

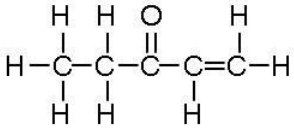
Methyl vinyl ketone



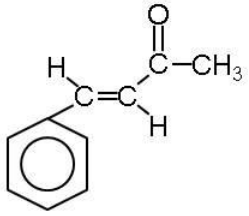
Cyclohexene-1-one



Ethyl vinyl ketone



Methyl styryl ketone



Compounds studied under the α, β-unsaturated ketone initiative

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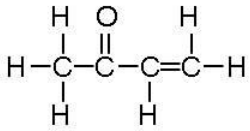
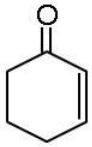


Cyclohexene-1-one



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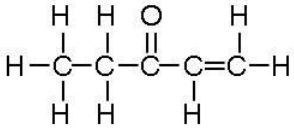
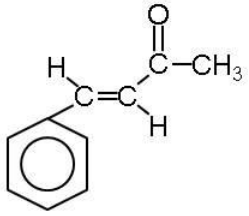


Methyl styryl ketone



Compounds studied under the α, β-unsaturated ketone initiative

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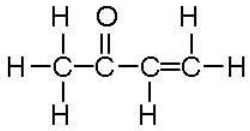
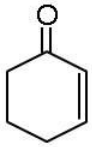


Cyclohexene-1-one



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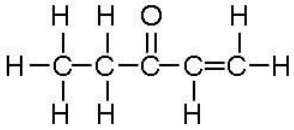

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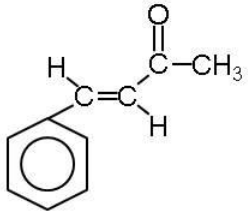

Experimental design of 90-day feed studies of MSK

B6C3F1 Mice M & F	F344 Rats M & F
% in diet	% in diet
0	0
0.025	0.025
0.05	0.05
0.1	0.1
0.2	0.2
0.4	0.4

n=10 per group

Results of 90-day feed studies of MSK

F344 Rats

- Kidney: Minimal to mild nephropathy at 0.2% and 0.4% in male rats
- Nose: Treatment-related hyperplasia of the goblet cells of the respiratory epithelium

B6C3F1 Mice

- Nose: Atrophy of the olfactory epithelium at 0.2% (one male) and 0.4% (all mice)

Experimental design of 90-day dermal studies of MSK

F344 Rats M & F	B6C3F1 Mice M & F
Dermal Dose (mg/kg)	Dermal Dose (mg/kg)
Vehicle (95% ethanol)	Vehicle (95% ethanol)
22	87.5
44	175
87.5	350
175	700
350	1,400

n=10 per group

Results of 90-day dermal studies of MSK

F344/N Rats

- All rats survived to study termination.
- Mean body weights were similar to that of the vehicle control groups.

Results of 90-day dermal studies of MSK

F344/N Rats

- Skin, site of application: dose related increases in the incidences of the following in males and females:
  - Epidermis, hyperplasia
  - Inflammation, chronic-active
  - Hyperkeratosis
  - Sebaceous gland hypertrophy
- Skin, site of application – Ulcer and/or Necrosis in the 175 and 350 mg/kg dose groups of both sexes
- Nose, respiratory epithelium – Hyperplasia, goblet cell:
  - Males: 350 mg/kg
  - Females: all doses

Results of 90-day dermal studies of MSK

B6C3F1 Mice

- All mice in the 700 and 1400 mg/kg dose groups of both sexes died by the end of week 3 of the study.
  - These mice were euthanized due to severe skin lesions (ulceration and necrosis) at the site of application.
  - All other mice survived to study termination.
- Mean body weights of the surviving mice were similar to that of the vehicle control groups.

Results of 90-day dermal studies of MSK

B6C3F1 Mice

- Skin, site of application: dose related increases in the incidences of the following in males and females:
  - Epidermis, hyperplasia
  - Inflammation, chronic-active
  - Hyperkeratosis
  - Sebaceous gland hypertrophy
  - Hair follicle hyperplasia
- Skin, site of application – Ulcer and/or Necrosis
  - Males: 87.5 (1 animal), 700, and 1400 mg/kg dose groups
  - Females: 700 and 1400 mg/kg dose groups
- Nose, olfactory epithelium – Atrophy: Treatment-related increase at 350, 700, and 1,400 mg/kg in males and females

Recovery of ^{14}C-methyl *trans*-styryl ketone in male F344/N rats

	% of Radioactive Dose Recovered[a]				
Route	Urine	Feces	Tissues	Trap & Skin Site[b]	Total Recovery[c]
IV (20 mg/kg)	95.5 ± 1.5	2.7 ± 0.5	0.4 ± 0.03	_	98.6 ± 1.5
Oral (200 mg/kg)	96.6 ± 0.6	4.8 ± 0.3	0.1 ± 0.02	_	101.5 ± 0.9
Dermal (250 mg/kg)	55.0 ± 11.5	1.2 ± 0.3	0.3 ± 0.1	39.8 ± 9.3	96.3 ± 2.1

[a] Mean % of dose ± SD, n=3; oral and IV studies were conducted for 48 hours, whereas the dermal study was conducted for 120 hours

[B] Includes skin trap, activated charcoal and skin at the site of application

[c] Exhaled radioactive CO_2 and organics accounted for <0.6% of the total dose; data not included in total recovery

Experimental design of 2-year dermal studies of MSK

F344 Rats M & F	B6C3F1 Mice M & F
Dermal Dose (mg/kg)	Dermal Dose (mg/kg)
Vehicle (95% ethanol)	Vehicle (95% ethanol)
10	10
30	30
90	90

n=50 per group

Results of 2-year dermal studies of MSK

F344/N Rats

- Survival was similar to controls.
- Mean body weights were within 10% of the vehicle control groups.
- No treatment-related neoplasms were observed at the site of application or elsewhere.

Non-neoplastic lesions in 2-year dermal rat study

Skin, Site of Application				
MSK (mg/kg):	**0**	**10**	**30**	**90**
Males				
Epidermis, hyperplasia	0	3 (1.0)[a]	3 (1.0)	29** (1.0)
Hyperkeratosis	20 (1.1)	13 (1.0)	33** (1.2)	47** (2.4)
Females				
Epidermis, hyperplasia	1 (1.0)	1 (1.0)	5 (1.0)	39** (1.2)
Hyperkeratosis	9 (1.1)	11 (1.0)	20* (1.0)	47** (2.3)

n = 50
*p ≤ 0.05, **p ≤ 0.01
[a] Numbers in parentheses indicate average severity grades: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

Non-neoplastic lesions in 2-year dermal rat study

Nose

MSK (mg/kg):	0	10	30	90
Males				
Fungus 2	9*	11**	12**	
Inflammation, chronic	25 (1.6)[a]	24 (2.0)	31 (1.7)	30 (2.1)
Olfactory epithelium – Metaplasia, respiratory	7 (1.3)	13 (1.3)	6 (1.8)	12 (1.5)
Respiratory epithelium – Hyperplasia	19 (1.4)	18 (1.9)	18 (1.7)	23 (2.0)
Respiratory epithelium – Metaplasia, squamous	3 (2.3)	7 (2.1)	15** (2.3)	13** (2.1)

n = 50
*p ≤ 0.05, **p ≤ 0.01
[a] Numbers in parentheses indicate average severity grades: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

Results of 2-year dermal studies of MSK

B6C3F1 Mice

- Survival was similar to controls.
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Non-neoplastic lesions in 2-year dermal mouse study

Skin, Site of Application				
MSK (mg/kg):	**0**	**10**	**30**	**90**
Males				
Epidermis, hyperplasia	7 (1.1)[a]	13 (1.5)	29** (1.2)	37** (1.6)
Hyperkeratosis	17 (1.2)	19 (1.7)	26 (1.3)	40** (1.6)
Hyperplasia, melanocyte	0	1 (1.0)	23** (1.2)	44** (2.2)
Inflammation, chronic	1 (1.0)	8* (1.4)	15** (1.2)	43** (1.7)
Ulcer 0	2 (3.0)	2 (3.5)	5* (1.6)	

n = 50
*p ≤ 0.05, **p ≤ 0.01
[a]Numbers in parentheses indicate average severity grades: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

Non-neoplastic lesions in 2-year dermal mouse study

Skin, Site of Application

MSK (mg/kg):	0	10	30	90
Females				
Epidermis, hyperplasia	7 (1.3)[a]	11 (1.0)	31** (1.5)	33** (1.7)
Hyperkeratosis	9 (1.4)	16 (1.4)	37** (1.6)	36** (1.7)
Hyperplasia, melanocyte	3 (1.0)	3 (1.0)	33** (1.2)	36** (2.1)
Inflammation, chronic	7 (1.3)	11 (1.3)	33** (1.5)	38** (1.6)
Ulcer 0	0	2 (2.5)	4 (3.3)	

n = 50
*p ≤ 0.05, **p ≤ 0.01
[a]Numbers in parentheses indicate average severity grades: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

Non-neoplastic lesions in 2-year dermal mouse study

MSK (mg/kg):	0	10	30	90
Eye (Males)				
Inflammation, chronic-active	0	1 (2.0)[a]	1 (2.0)	4 (2.8)
Cornea, hyperplasia	0	1 (2.0)[a]	1 (2.0)	4 (3.0)
Skin, Control (Males)				
Hyperkeratosis	1 (2.0)	3 (2.7)	1 (1.0)	5 (1.0)
Inflammation, chronic	0	3 (2.0)	2 (1.0)	6* (1.0)
Epidermis, hyperplasia	0	2 (3.5)	0	4 (1.0)
Skin, Control (Females)				
Hyperkeratosis	3 (2.7)	4 (1.3)	3 (1.0)	12* (1.4)
Inflammation, chronic	1 (1.0)	4 (1.3)	7 (1.0)	18** (1.2)
Epidermis, hyperplasia	2 (3.0)	2 (1.0)	2 (1.5)	9* (1.2)

n = 50
*p ≤ 0.05, **p ≤ 0.01
[a]Numbers in parentheses indicate average severity grades: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

Conclusions of the 2-year dermal studies of MSK

- There was **no evidence of carcinogenic activity** of methyl trans-styryl ketone in male and female F344/N rats following dermal exposure.
- There was **no evidence of carcinogenic activity** of methyl trans-styryl ketone in male and female B6C3F1 mice following dermal exposure.
- There were nonneoplastic lesions such as epidermal hyperplasia and hyperkeratosis at the site of application in male and female rats and mice.
- There was systemic exposure to methyl trans-styryl ketone following dermal exposure based on the tissue distribution data.